FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT [redacted] MMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY DOCKET NUMBER	
5808-01-CA	

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
09/980965	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/05783	07 June 2000	07 June 1999

TITLE OF INVENTION
TRICYCLIC ANALGESICS

APPLICANT(S) FOR DO/EO/US
CALVET, Alain; JACOBELLI, Henri; PUAUD, Jocelyne; ROMAN, Francois J.; HAMON, Jacques; GROUHEL, Agnes

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☒ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Published PCT specification (WO 00/75116)

Express Mail No. EF378134286US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 [illegible] 09/980995	INTERNATIONAL APPLICATION NO. PCT/EP00/05783	ATTORNEY'S DOCKET NUMBER 5808-01-CA

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☒	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$1,040.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	13 - 20 =	0	x $18.00	**$0.00**
Independent claims	4 - 3 =	1	x $84.00	**$84.00**
Multiple Dependent Claims **(check if applicable)**			☒	**$280.00**
	TOTAL OF ABOVE CALCULATIONS =			**$1,404.00**
☐	Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.			**$0.00**
	SUBTOTAL =			**$1,404.00**
	Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +			**$0.00**
	TOTAL NATIONAL FEE =			**$1,404.00**
☐	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			**$0.00**
	TOTAL FEES ENCLOSED =			**$1,404.00**
				Amount to be: refunded $
				charged $

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **23-0455** in the amount of **$1,404.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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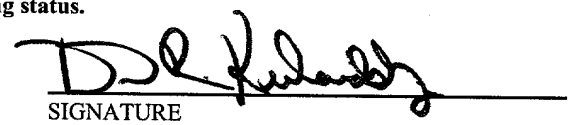


SIGNATURE

David R. Kurlandsky
NAME

41,505
REGISTRATION NUMBER

04 December 2001
DATE

TRICYCLIC ANALGESICS

FIELD OF THE INVENTION

The invention relates to organic compounds characterized as having a fused bicyclic ring system substituted with a spiro nitrogen-containing third ring. The compounds are effective for treating seizures and chronic pain in mammals.

BACKGROUND OF THE INVENTION

Although chronic pain is a frequent condition in the population, its pathophysiology is not well understood. One possibility is that nociceptive spinal sensory neurons generate inappropriate activity after injury. Spinal sensory neurons become hyperexcitable and generate spontaneous impulses after injury in experimental animals, and in humans. Matzner and Devor (1992) proposed that the hyperexcitability associated with chronic pain results from an increase of Na channel density at the site of injury. It has also been hypothesized that, after nerve injury, changes in the kinetics and voltage-dependent characteristics of Na currents contribute to the ectopic impulse generation and hyperexcitability of spinal sensory neurons. Dorsal root ganglion (DRG) neurons possess a complex mix of Na currents, including a fast tetrodotoxin-sensitive (TTX-S) current and a slow TTX-resistant (TTX-R) current. In rat DRG neurons, PGE_2, adenosine and serotonin, three agents that produce hyperalgesia in vivo, increase the magnitude of the TTX-R current, and shift its conductance/voltage relationship in a hyperpolarized direction (Gold *et al.*, 1996). Following nerve injury, TTX-R currents are down regulated in DRG neurons, and, in the same animals, TTX-S currents are upregulated (Cummings and Waxman, 1997). Using a Na channel specific antibody, Devor *et al.* (1993) evidenced an accumulation of Na channels in the neuroma resulting from a nerve section; the accumulation of Na channels at injured axonal tips may explain the ectopic channel excitability and the resulting

pain and paresthesia which frequently complicate peripheral nerve injury in humans.

Injury to the axons of spinal sensory neurons appear to modify Na currents, substantially altering their excitability; Thus, selective blockers of Na channels can be used for the prevention or treatment of chronic pain in mammals. Sodium channel blockers have been shown effective in chronic pain syndromes, including trigeminal neuralgia, diabetic neuropathy, migraine prophylaxia and cancer pain (review by McQuay *et al.* ,1995, British Medical Journal, 1995; **311**: 1047-1052, and references cited therein).

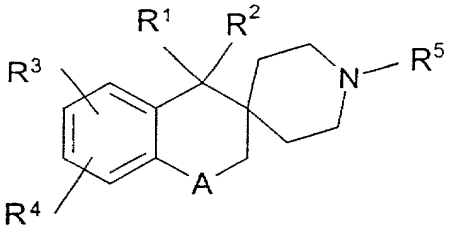
However, pain due to acute or chronic nerve injury is difficult to treat, and is often resistant to conventional analgesics. Such compounds include some local anesthetics and anticonvulsants, for example lidocaine, etidocaine, benzocaine, tetracain, riluzole, phenytoin, and gabapentin. Most of them, even though such agents modulate Na channels, have limited clinical use because of high risks of adverse events. Lidocaine, for example, can cause cardiovascular collapse and resultant cardiac arrest. Benzocaine, can cause respiratory distress, as well as skin rash, erythema and oedema. The use of phenytoin for seizure disorders can result in hyperglycemia.

Because there is no effective chemical treatment for neuropathic pain, e.g. chronic pain, and since such pain is typically associated with diseases such as cancer, as well as severe physical injuries and diabetic neuropathy, the need continues to find compounds which can be utilized clinically without resulting in severe adverse events.

SUMMARY OF THE INVENTION

The inventors have now discovered a series of tricyclic compounds which are potent antagonists of neuronal Na channels. The compounds are characterized as fused bicyclic ring systems having a spiro third ring substitution.

The invention therefore provides tricyclic compounds of Formula I:



(I)

wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen or hydroxy; or

R^1 and R^2 together are oxygen ;

A is a bond, CH_2, CH CH_3, CH_2 CH_2 or $C(CH_3)_2$;

R^3 and R^4 are the same or different and are hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, trifluoromethyl, NO_2, COR^6, $COOR^6$ or NR^6R^7, wherein R^6 and R^7 are the same or different and are hydrogen, C_1-C_6 alkyl or benzyl ;

R^5 is hydrogen, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{3\text{-}6}$ cycloalkyl, (O=C)-$C_{1\text{-}6}$ alkyl, (O=C)- $C_{2\text{-}6}$ alkenyl, (O=C)-$C_{3\text{-}6}$ cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl,

and the pharmacentically acceptable salts thereof.

The compounds of the invention are useful in the clinical management and treatment of various conditions such as seizure disorders, epilepsy, neuroprotection, preferably for conditions such as cerebral ischemia, hypoxia and head trauma, local anesthesia, pain, preferably acute, chronic, neuropathic, visceral and somatic pain, irritable bowel syndrom (IBS), the treatment of drug dependence, migraine and obsessional compulsive disorders.

Preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group and R^3 is hydrogen or C_1-C_4 alkoxy.

Most preferred compounds of the invention are compounds of Formula I wherein R^1 and R^2 together are oxygen and A is CH_2.

Other most preferred compounds are those of formula I wherein R^5 is H, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group and R^3 is hydrogen or C_1-C_4 alkoxy.

Another embodiment of this invention is a pharmaceutical formulation comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier or diluent.

A further embodiment of the present invention is a method for treating a mammal suffering from pain and in need of treatment, comprising administering an effective amount of a compound of Formula I.

Still another embodiment of the invention is a method for treating a seizure disorder in a mammal in need of treatment, comprising administering a compound of Formula I.

Methods of treatment of all the further indications referred to above also fall within the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C_1-C_6 alkyl" means a straight or branched carbon chain made up of from one to six carbon atoms. Examples of C_1-C_6 alkyl groups include methyl, ethyl, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl and *n*-hexyl.

"C_1-C_6 alkoxy" means the foregoing alkyl groups bonded through oxygen, for example methoxy, isopropoxy, and *n*-hexyloxy.

"C_2-C_6 alkenyl" means a straight or branched carbon chain having from two to six carbon atoms, with one carbon-carbon double bond present in the chain. Examples include ethenyl, 2-propenyl, 1-methyl-3-pentenyl, 1-ethyl-2-butenyl, and 5-hexenyl.

"C_3-C_6 cycloalkyl" means a non-aromatic cyclic ring having from three to six carbon atoms, examples being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The foregoing alkyl, alkenyl and cycloalkyl groups may be substituted by 1, 2 or 3 groups selected from halo, unsubstituted C_3-C_6 cycloalkyl, phenyl or substituted phenyl. "Halo" means chloro, bromo, fluoro and iodo. "Substituted phenyl" means a phenyl group having 1, 2 or 3 substituents selected from halo, hydroxy, nitro, unsubstituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and NH_2.

Examples of C_1-C_6 alkyl groups substituted with cycloalkyl thus include cyclopropylmethyl, 1-cyclobutylethyl, 3-cyclohexylbutyl and 3,3-dicyclohexylpropyl. Alkyl groups substituted with halo include chloromethyl, 1,2-dibromoethyl, trifluoromethyl, and 1-bromo-3-chloro-6-iodohexyl. Alkyl groups substituted with phenyl or with substituted phenyl include benzyl, 1-phenylpropyl, 1-methyl-3-phenyl-butyl, 3-chlorophenylmethyl, 2,3-dimethoxybenzyl, 3-(2-methyl-5-fluoro-6-nitrophenyl)-butyl, and 3,3-diphenylpropyl.

Examples of substituted C_2-C_6 alkenyl groups include 2-cyclobutylethenyl, 3-phenyl-2-butenyl, 1,1-dimethyl-3-chloro-3-butenyl, 4,4-diphenyl-3-butenyl, 2-

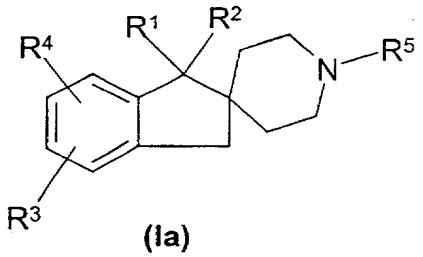
(3-chlorophenyl)-3-cylclobutyl-4-hexenyl, and 1,2-difluoro-3-(2-phenyl-cyclobutyl)-4-pentenyl.

Examples of substituted C_3-C_6 cycloalkyl groups include 3-cyclopentylcyclohexyl, 2-phenylcyclobutyl, 3-chlorocyclopentyl, 2,2-dibromo-3-nitrocyclohexyl, and 2,2-di-(3-methoxyphenyl)-cyclopropyl.

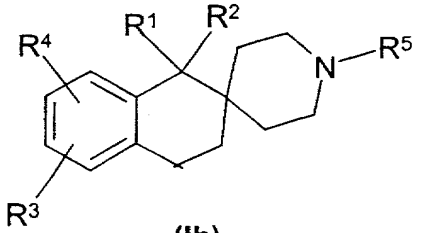
Examples of substituted C_1-C_6 alkoxy groups include trichloromethoxy, cyclopropylmethoxy, 1-methyl-2-phenylpropoxy and 2,3-di-(2,4-dinitrophenyl)-hexyloxy.

The alkyl, alkenyl and cycloalkyl substituent groups can be bonded through a carbonyl (O=C) group. Examples include acetyl, pivaloyl, 1-oxo-3-pentenyl, 1-oxocyclobutylmethyl, 1-oxo-3-phenyl-4-cyclohexylpentyl, and 1-oxo-(3-phenylcyclopentyl)-methyl.

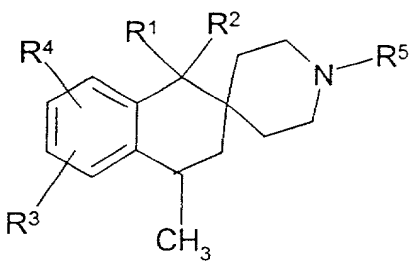
"-A-" in Formula I is defined as a bond, $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)_2$ and $-CH_2CH_2-$; the invention compounds can thus have the following general structures:



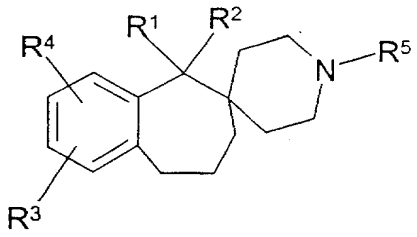
(Ia)



(Ib)



(Ic)



(Id)

Preferred compounds of the present invention include the following:

3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;

3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

More preferred compounds of the invention include the following:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

Most preferred compounds of the invention include the following:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

The compounds of Formula I are characterized by being bicyclic rings having a spiro ring as a substituent group. The spiro ring contains a nitrogen atom (i.e. N-R^5), which can be basic in nature when R^5 is a group such as alkyl, alkenyl or cycloalkyl. Such basic compounds readily form pharmaceutically acceptable salts by reaction with common inorganic and organic acids. Typical acids utilized to form the pharmaceutically acceptable salts of the invention include hydro-

chloric, sulfuric, sulfamic , phosphoric , citric , succinic , glutamic , maleic , lactic, tartaric, *p*-toluenesulfonic, benzoic , oxalic and salicyclic acid. The salts are prepared by simply contacting the spiro base with the appropriate acid, generally in a solvent such as methanol or diethyl ether. The salts generally are highly crystalline, readily precipitate, and are recovered by filtration. They can be further purified if desired by recrystallization from common solvents such as methanol, ethyl acetate, acetone and tetrahydrofuran.

The invention compounds of Formula I are readily prepared by methodologies well known in the art of organic chemistry. It is preferred to simply first prepare a compound wherein R^5 is hydrogen, and then react this compound with R^5-alkylating or -acylating agents. Such reaction is shown in scheme 1 below :

Scheme 1

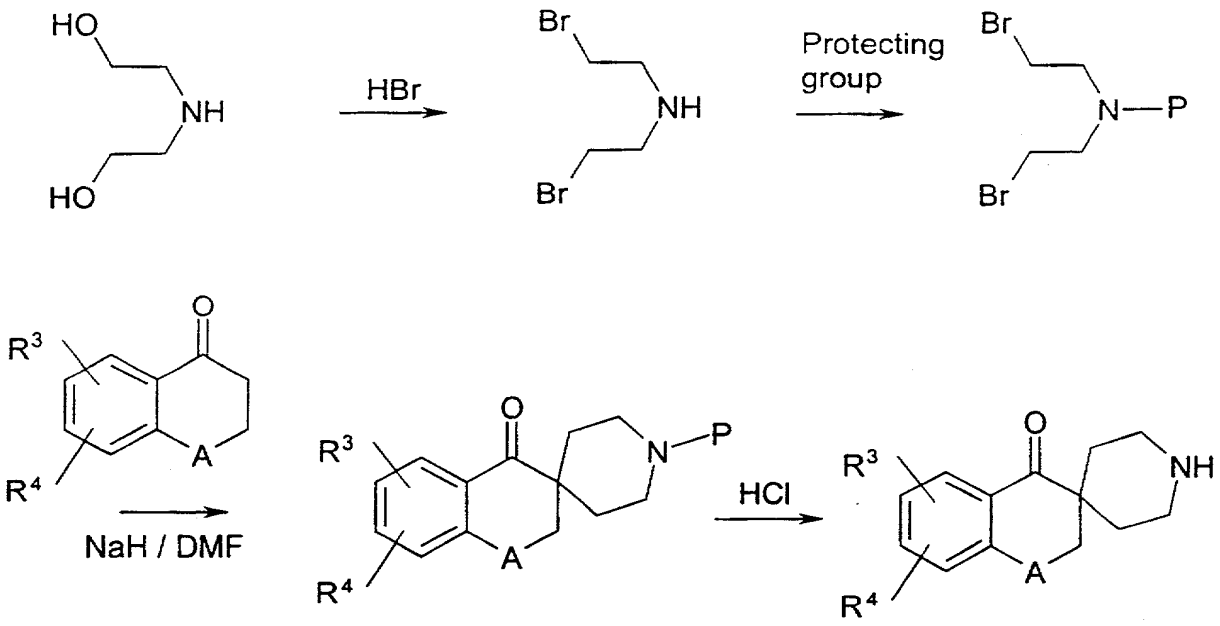
where R^1 , R^2 , R^3 , R^4 , and A have the meanings given above, and " L " is a normal leaving group (e.g. halo such as chloro or bromo, or a silyl derivative such as trimethylsilyl).

The foregoing reaction is carried out by combining approximately equimolar quantities of the spiro amine with the alkylating or acylating agent (i.e. L-R^5), generally in an unreactive organic solvent such as tetrahydrofuran, dimethylsulfoxide, or N,N-dimethylformamide. A base such as triethylamine or $NaHCO_3$ can be utilized to act as an acid scavenger if desired. The reaction typically is substantially complete after about 2 - 20 h, when conducted at a temperature is about 25°C to about 60°C. The product is readily isolated by removing the reaction solvent, and further purification can be achieved if desired by normal means such as salt formation, crystallization, and chromatography.

The required starting material, i.e. the spiro amine, can be synthesized from readily available reactants, utilizing any of several methods:

-In one method, an N-protected form of a derivatized diethylamine is reacted with a bicyclic ketone according to scheme 2:

Scheme 2

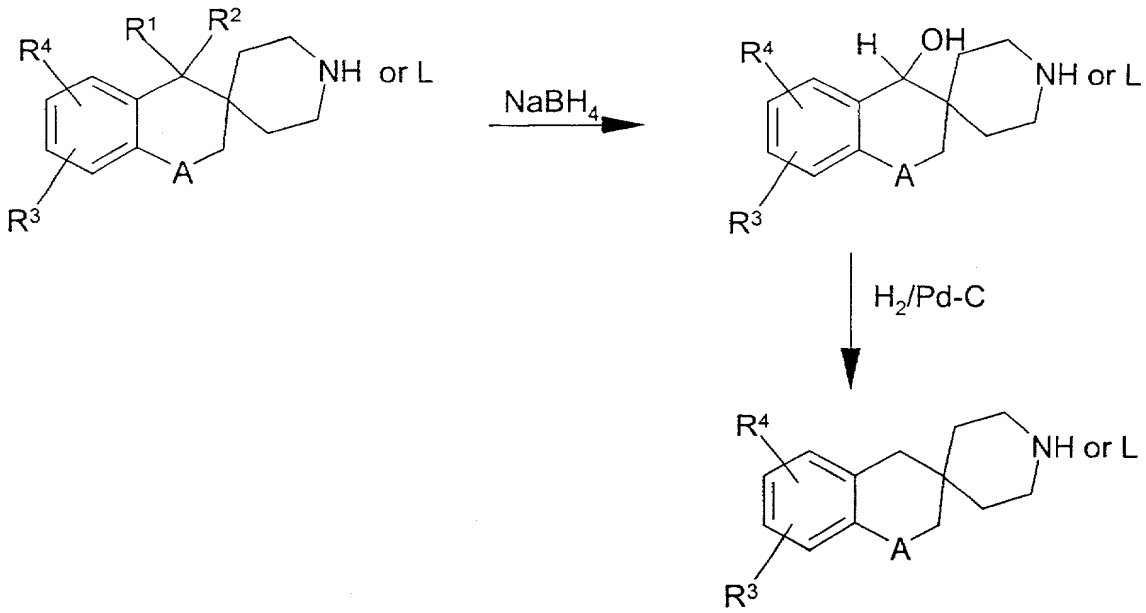


In the above scheme 2, P is an amine-protecting group that is easily removed, for example ethoxycarbonyl or benzyl. The protected diethylamine derivative is readily reacted with a bicyclic ketone in the presence of a strong base such as NaH. This reaction results in formation of the spiro amino derivative, which is readily de-protected by conventional means, for instance by reaction with hydrochloric acid.

Scheme 2 illustrates the preparation of keto substituted starting materials, i.e. where R^1 and R^2 together are oxo. Such compounds are easily converted to the corresponding alcohol (R^1 is H , R^2 is OH) by reaction with a reducing agent such as $NaBH_4$, generally in a solvent such as methanol or ethanol.

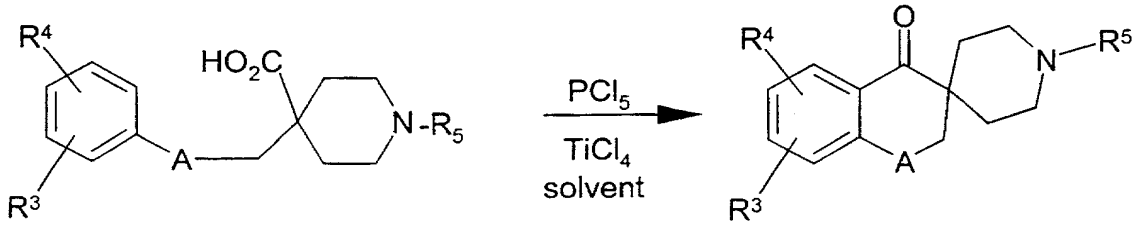
The alcohol can be further reduced by catalytic hydrogenation, for example by reaction with hydrogen gas in the presence of 10% palladium on carbon. These reactions are illustrated in Scheme 3 :

Scheme 3



The invention compounds of Formula I can alternatively be prepared by starting with a suitably substituted piperidine derivative, as shown in Scheme 4 :

Scheme 4

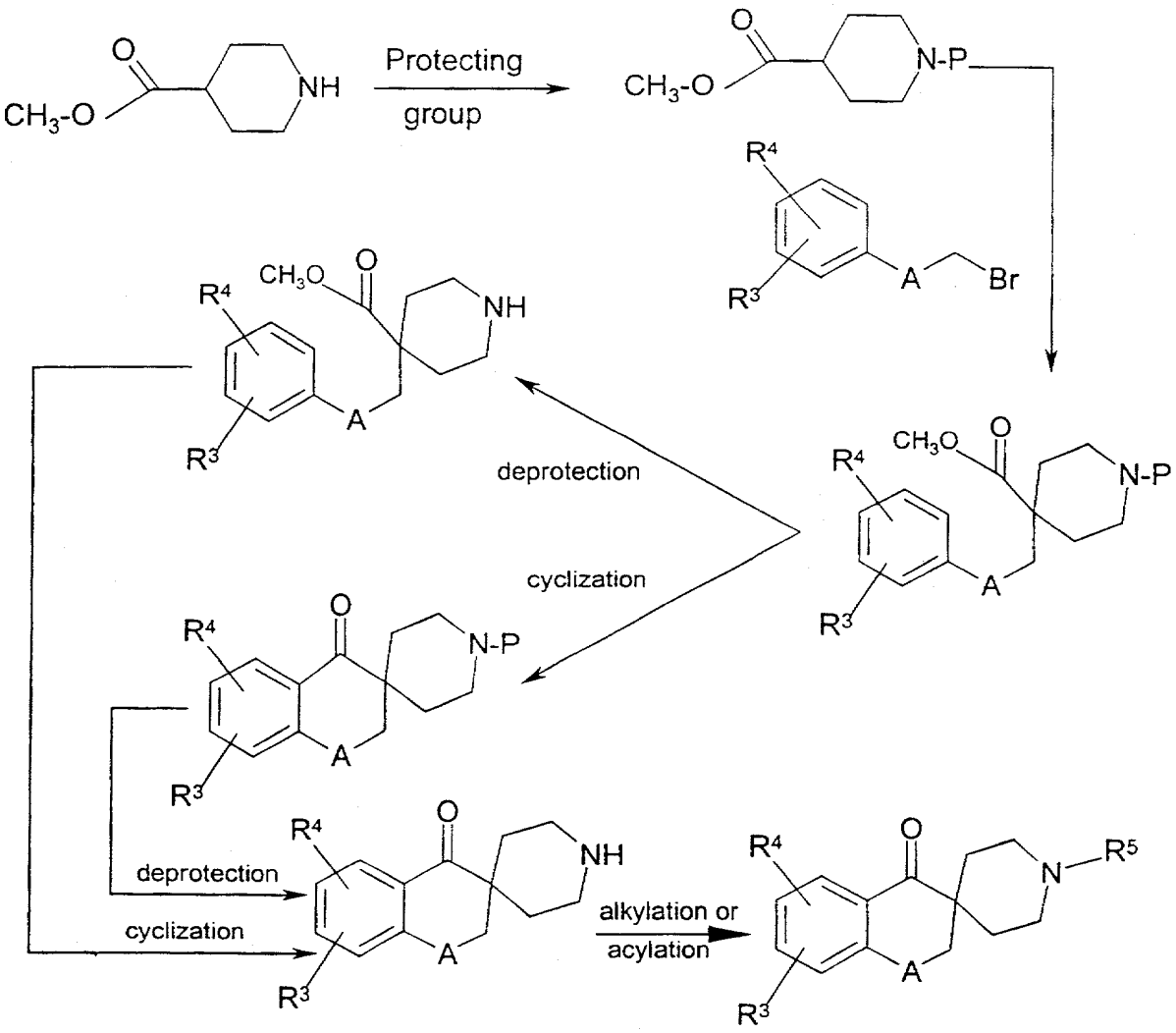


The cyclization reaction is accomplished by reacting the substituted piperidine with strong dehydrating agents such as phosphorus pentachloride and titanium tetrachloride, generally in an unreactive organic solvent such as benzene, toluene, xylene, or chloroform. The reaction normally is complete within 2 h when carried out at a temperature of 30°C to 60°C.

The cyclized product is a compound of Formula I wherein R^1 and R^2 together are oxo, which, as noted above in Scheme 3, can be reduced to the corresponding alcohol or alkane (R^1 and R^2 both hydrogen).

The substituted piperidine required for the above reaction is readily prepared as shown in Scheme 5:

Scheme 5



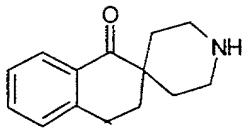
In Scheme 5, the methyl 4-piperidine formate is reacted with an amine-protecting agent (i.e. to insert P). Typical amine-protecting groups include *tert*-butoxy carbonyl, benzyl and trimethylsilyl. The protected piperidine derivative is next

reacted with a phenyl alkyl halide, for example phenylethyl bromide (where A is CH_2) or 2-phenylpropyl iodide (where A is $CH\text{-}CH_3$) or 3-phenylpropyl iodide (where A is $CH_2\ CH_2$), in the presence of a strong base such as NaH or lithium diisopropylamide (LDA), generally in an unreactive solvent such as tetrahydrofuran, or benzene. The reaction, carried out at about –20°C, generally is substantially complete after about 2 - 4 h. The alkylated piperidine can then be deprotected (removal of the L-protecting group) and cyclized by reaction with PCl_5 and $TiCl_4$, or it can be cyclized first, and the L-protecting group subsequently removed.

The following detailed examples illustrate the synthesis of specific compounds provided by this invention. The examples are representative only, and are not intended to be limiting in any respect.

EXAMPLE 1

3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: Bis(2-bromoethyl)amine hydrobromide.

157.5 g (1.5 mol) of diethanolamine and then, with stirring, 1.35 l of 48% HBr (exothermic reaction) are introduced into a 2 l three-necked flask which can be equipped either for reflux or for distillation. The solution is heated at a bath temperature of 180-200°C, in order to distill off a volume of 350 ml at a vapour temperature of 122°C. The device is adjusted to the reflux position and is maintained for 1 h. A further distillation is carried out as above, in order to collect a distillate of 465 ml. The device is again adjusted for reflux for 3.75 h and then 400 ml are distilled off. The mixture is cooled and 300 ml of ethyl acetate are added to the residue. The suspension is stirred for 1 h in an ice bath. The precipitate is filtered off and then washed with ethyl acetate. 367 g of a white crystalline product are obtained. Yd = 78.5%, M.p. (°C) = 130-135°C.

Stage 2: Ethyl bis(2-bromoethyl)carbamate.

367 g (1.17 mol) of the product obtained in the preceding stage and then 108 ml, i.e. 122.6 g (1.13 mol), of ethyl chloroformate are added, with stirring, to a 4 l reactor containing 1.8 l of a water/ice mixture. Approximately 1.3 l of a 2N sodium hydroxide solution are run into the solution over 5 min in order to achieve a continuing pH of 11, while maintaining a temperature below 5°C. The mixture is stirred for 5 min and then acidified to pH 1 with concentrated HCl. Extraction is carried out with 3 times 1 l of ethyl ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na_2SO_4. The solvent is evaporated. The residue is chromatographed by eluting with CH_2Cl_2. 208.5 g of product are obtained. Yd = 58%, TLC (CH_2Cl_2): R_f = 0.6,
N.M.R.: $CDCl_3$ ^1H ((ppm): 1.2 (t, 3H), 3.4-3.55 (m, 4H), 3.6-3.7 (m, 4H), 4.1-4.2 (q, 2H)).

Stage 3: Ethyl 3,4-dihydro-1-oxospiro [naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate.

69 g (0.472 mol) of 1-tetralone and 234 ml of DMF, dried beforehand over molecular sieve, are introduced into a reactor which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -15°C with a dry ice/acetone bath and 34.6 g (1.15 mol) of 80% sodium hydride, as a dispersion in mineral oil, are added thereto. The temperature is allowed to rise to approximately 20-25°C (exothermic reaction). The reaction mixture is stirred for 1.5 h at a temperature below 30°C.

At the same time, a solution of 208 g (0.69 mol) of ethyl bis(2-bromoethyl)carbamate in 234 ml of DMF (dried beforehand over molecular sieve) is cooled, in a reactor which is protected from moisture and which is under an inert atmosphere, to -25°C with a dry ice/acetone bath. The reaction liquors, prepared at the same time, are introduced by transfer under nitrogen and run in over 10 min at a temperature of -25°C. The temperature is allowed to rise (exothermic reaction with rise in the temperature to 45°C). The reaction mixture is then cooled in order to maintain it at approximately 30°C. It is subsequently

brought to 50°C for 2 h and then the solvent is evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 1.2 l of ice-cold water and extracted with 3 times 600 ml of ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na_2SO_4. After evaporating the solvent, a dark brown oily residue is obtained which is purified by fast chromatography by eluting with CH_2Cl_2 gradually enriched with acetone. 57.7 g (0.2 mol) of product are obtained (Yd = 42.5%), TLC (97/3 CH_2Cl_2/acetone): R_f = 0.45.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.85-2.95 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

Stage 4: 3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine).

57.7 g (0.2 mol) of ethyl 3,4-dihydro-1-oxospiro-[naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate and then 1.6 l of 6N HCl are introduced into a reactor. The mixture is stirred and brought to reflux for 14 h. It is then cooled and extracted with twice 500 ml of ethyl ether. The aqueous phase is basified while cold with NaOH and extracted with 3 times 500 ml of ethyl ether. The organic phase is washed and dried over Na_2SO_4. After evaporating the solvent, the residue is purified by chromatography by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH.

Weight: 31 g, Yd = 72%, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.2-0.35.

N.M.R.: $CDCl_3$ ^1H ((ppm) Base: 1.35-1.45 (m, 2H), 1.8-1.9 (m, 2H), 2.0 (t, 2H), 2.1 (s, 1H), 2.75-2.85 (m, 2H), 2.85-3.0 (m, 4H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized from a methanol/ether mixture.

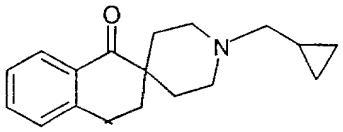
White powder, M.p. = 235°C, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): $R_f = 0.35$.

Analysis conforms to $C_{14}H_{18}ClNO$.

IR: 2995, 2700, 1675, 1600, 1440, 1395, 1210, 1090, 990, 750, 740 cm^{-1}

EXAMPLE 2

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



10 g (46.4 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] and then 80 ml of DMF and 36.2 ml of THF are introduced into a three-necked flask. 6.89 g (51 mmol) of (bromomethyl)cyclopropane and 7.8 g (92.8 mmol) of $NaHCO_3$ are added. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 200 ml of water and extracted with 3 times 100 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 100 ml of ether. The organic phase is washed with an NaCl solution and dried over Na_2SO_4. Once the solvent has been evaporated, 12 g of an oily residue are obtained. The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized by addition of 20 ml of ether to a methanolic solution of the product, crystallization is allowed to take place overnight at 20-25°C and then the product is filtered off and washed with water. After drying, 8.4 g of product are obtained.

White powder, M.p. = 243°C, TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): $R_f = 0.55$.

Analysis conforms to $C_{18}H_{24}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.55 (m, 2H), 0.75-0.8 (m, 2H), 1.3-1.4 (m, 1H), 2.1-2.2 (m, 4H), 2.4-2.55 (m, 2H), 2.85-2.9 (m, 2H), 3.0-3.05 (m, 2H), 3.2-

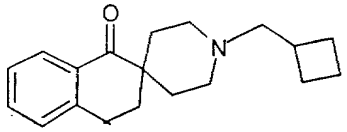
3.3 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.25 (m, 1H), 7.3-7.35 (m, 1H), 7.5-7.6 (m, 1H), 7.95-8.0 (m, 1H), 12.0-12.2 (m, 1H).

IR: 2990, 2700, 1675, 1600, 1420, 1395, 1320, 1080, 980, 900, 760, 740 cm^{-1}

The corresponding iodomethylate was also obtained. MP: 162°C

EXAMPLE 3

1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using cyclobutylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 235°C.

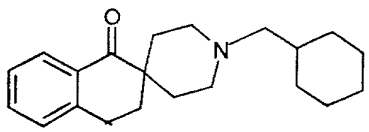
TLC: (92/8 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.7. Analysis conforms to $C_{19}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 1.8-2.25 (m, 10H), 2.4-2.5 (m, 2H), 2.95-3.1 (m, 5H), 3.1-3.25 (m, 2H), 3.25-3.35 (m, 2H), 7.2-7.35 (m, 2H), 7.45-7.55 (m, 1H), 7.9-8.0 (m, 1H), 11.95-12.15 (m, 1H))

IR: 3400, 2900, 2650, 2500, 1680, 1590, 1430, 1360, 1300, 1220, 1140, 1100, 1040, 960, 930, 900, 800, 770, 740, 640 cm^{-1}

EXAMPLE 4

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using cyclohexylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 265°C.

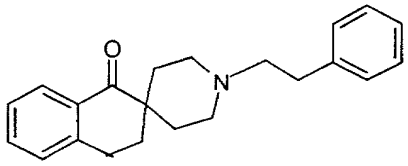
TLC: (93/7 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.8. Analysis conforms to $C_{21}H_{30}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.95-1.3 (m, 5H), 1.6-2.1 (m, 10H), 2.5-2.65 (m, 2H), 2.7-2.8 (m, 2H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 2H), 3.3-3.4 (m, 2H), 7.15-7.3 (m, 2H), 7.4-7.5 (m, 1H), 7.9-7.95 (m, 1H), 11.6-11.8 (m,1H))

IR: 3400, 2900, 2500, 1680, 1600, 1440, 1360, 1300, 1220, 1150, 1110, 1060, 980, 910, 760, 735 cm^{-1}

EXAMPLE 5

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using phenethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = >275°C, Yd = 55%.

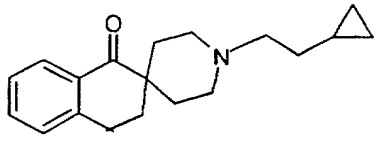
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.85. Analysis conforms to $C_{22}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.15 (m, 4H), 2.3-2.45 (m, 2H), 2.9-3.0 (m, 2H), 3.05-3.25 (m, 6H), 3.4-3.5 (m, 2H), 7.1-7.3 (m, 7H), 7.4-7.45 (m, 1H), 7.85-7.9 (m, 1H), 12.25-12.45 (m, 1H))

IR: 3400, 2900, 2500, 1670, 1600, 1450, 1360, 1290, 1220, 1110, 1010, 960, 820, 800, 740, 700 cm^{-1}

EXAMPLE 6

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



0.94 g (4.36 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] and then 10 ml of DMF are introduced into a three-necked flask. 1.3 g (8.7 mmol) of (bromoethyl)cyclopropane in 2 ml of DMF and then 0.73 g (8.7 mmol) of $NaHCO_3$ are added to the solution obtained. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are removed at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 50 ml of water and extracted with three times 50 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 50 ml of ether. The organic phase is washed with an NaCl solution and dried over Na_2SO_4. The solvent is removed. The oily residue is purified by fast chromatography by eluting with CH_2Cl_2 enriched with methanol. 0.6 g is obtained, the hydrochloride of which is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized by addition of 30 ml of ether to a solution of the product in 5 ml of isopropanol. Crystallization is allowed to take place for 14 h at 20-25°C and then the product is filtered off and washed with ether. After drying, 0.5 g of white powder is obtained, M.p. = 244°C,

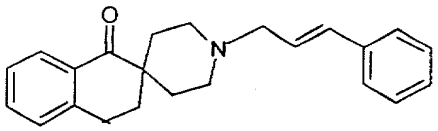
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.35. Analysis conforms to $C_{19}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.1-0.3 (m, 2H), 0.45-0.65 (m, 2H), 0.7-0.8 (m, 1H), 1.6-2.6 (m, 8H), 2.9-3.5 (m, 8H), 7.2-7.4 (m, 2H), 7.4-7.6 (t, 1H), 7.9-8.05 (d, 1H), 12.15 (1H))

IR: 2900, 2450, 1670, 1600, 1430, 1290, 1220, 950, 890, 740 cm^{-1}

EXAMPLE 7

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Prepared according to the method described in Example 2 with cinnamyl bromide, then purification by chromatography and crystallization of the hydrochloride. White powder, M.p. = 228°C.

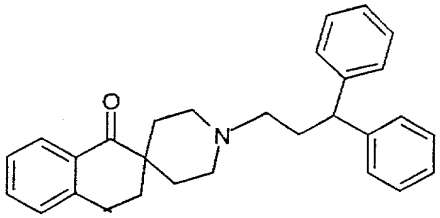
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.55. Analysis conforms to $C_{23}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.25 (m, 4H), 2.3-2.5 (m, 2H), 2.9-3.85 (m, 8H), 6.4-6.6 (m, 1H), 6.6-6.8 (d, 1H), 7.1-7.6 (m, 8H), 7.9-8.0 (d, 1H), 12.1 (1H))

IR: 2900, 2400, 1670, 1590, 1420, 1290, 1220, 970, 730, 690 cm^{-1}

EXAMPLE 8

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



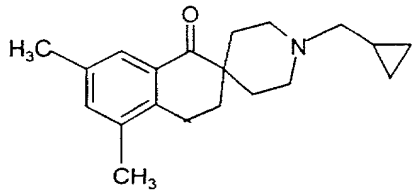
Prepared according to the method described in Example 6 with 3,3-diphenylpropyl bromide and preparation of the hydrochloride. A white powder is obtained, M.p. = 257°C, TLC (95/5 CH_2Cl_2/MeOH): R_f = 0.35. Analysis conforms to $C_{29}H_{32}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.2 (m, 4H), 2.4-3.5 (m, 12H), 3.9-4.05 (m, 1H), 7.2-7.4 (m, 12H), 7.4-7.6 (m, 1H), 7.9-8.0 (m, 1H), 12.3 (1H))

IR: 2900, 2350, 1670, 1590, 1450, 1300, 1220, 910, 740, 700 cm^{-1}

EXAMPLE 9

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] is prepared according to the methods described for the synthesis of Example 1. The "N" alkylation is identical to that described in Example 6. The hydrochloride is obtained in the form of a white powder, M.p. > 260°C.

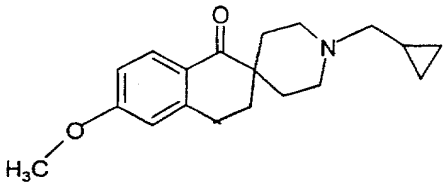
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.5. Analysis conforms to $C_{20}H_{28}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.3-0.4 (m, 2H), 0.7-0.8 (m, 2H), 1.1-1.3 (m, 1H), 2.0-2.1 (m, 4H), 2.2 (s, 3H), 2.3 (s, 3H), 2.35-2.45 (m, 2H), 2.7-2.85 (m, 4H), 3.0-3.2 (m, 2H), 3.4-3.5 (m, 2H), 7.15 (s, 1H), 7.6 (s, 1H), 12.15 (1H))

IR: 3400, 2900, 2500, 1670, 1605, 1470, 1430, 1280, 1180, 1020, 970, 950, 880, 830 cm^{-1}

EXAMPLE 10

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



By the process of Example 9, the hydrochloride is obtained.

White powder, M.p. > 255°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.35.

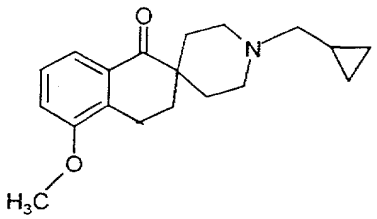
Analysis conforms to $C_{19}H_{26}ClNO_2$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-2.95 (m, 2H), 2.95-3.05 (m, 2H), 3.2-3.4 (m, 2H), 3.45-3.6 (m, 2H), 3.85 (s, 3H), 6.7 (s, 1H), 6.85 (d, 1H), 7.9-8.0 (d, 1H), 12.15 (1H))

IR: 2900, 2420, 1660, 1590, 1430, 1250, 1220, 960, 830, 600 cm^1

EXAMPLE 11

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Same process as for Example 10; the hydrochloride is obtained.

White powder, M.p. = 244°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.75.

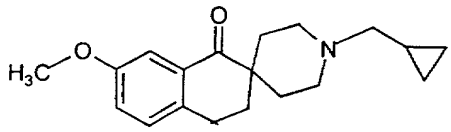
Analysis conforms to $C_{19}H_{26}ClNO_2$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.1-3.3 (m, 2H), 3.5-3.6 (m, 2H), 3.85 (s, 3H), 7.0-7.1 (m, 1H), 7.25-7.35 (m, 1H), 7.5-7.6 (m, 1H), 12.1-12.2 (1H))

IR: 2930, 2560, 2360, 1680, 1580, 1470, 1435, 1260, 1060, 970, 750 cm^{-1}

EXAMPLE 12

1'-(methylcyclo-propyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



By using the same methods as for Example 10, the hydrochloride is obtained.

White powder, M.p. = 235°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.70-0.75.

Analysis conforms to $C_{19}H_{26}ClNO_2$.

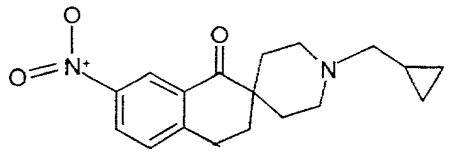
N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.2-3.3 (m, 2H), 3.5-3.6

(m, 2H), 3.80 (s, 3H), 7.0-7.1 (m, 1H), 7.15-7.25 (m, 1H), 7.4 (s, 1H), 12.1-12.2 (1H))

IR: 2930, 2510, 2445, 1670, 1610, 1495, 1415, 1250, 1025 cm^{-1}

EXAMPLE 13

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: 2.4 g (8.35 mmol) of ethyl 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate, prepared according to the method described in Stage 3 of Example 1, and 35 ml of concentrated sulphuric acid are introduced into a three-necked flask. 0.79 g (12.5 mmol) of fuming nitric acid is added to the solution cooled to 0°C. The mixture is stirred for 1 h at 0°C and then for 2 h at 20-25°C. The solution is precipitated from 100 ml of water and ice and then extracted with three times 100 ml of CH_2Cl_2. The organic phase is washed successively with water and saturated NaCl solution. After drying over Na_2SO_4 and evaporating the solvent, 2.75 g of an oil are obtained, which oil is chromatographed by eluting with CH_2Cl_2 gradually enriched with acetone. 1.5 g of ethyl 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*), 4'-piperidine]-1'-carboxylate are obtained in the form of an oily residue which crystallizes. Yd = 54%, TLC (98/2 CH_2Cl_2/acetone): Rf = 0.3.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.9-3.0 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.3 (d, 1H), 8.2 (d, 1H), 8.8 (s, 1H))

Stage 2: 1.5 g of the product of the preceding stage is hydrolysed by the process described in Stage 4, Example 1. After chromatography by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH, 0.45 g is isolated. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.1.

Stage 3: 0.22 g (0.845 mmol) of 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] obtained in the preceding stage is suspended in 3 ml of acetonitrile. A solution of 0.343 g (2.54 mmol) of cyclopropylmethyl bromide in 0.5 ml of acetonitrile is added with stirring. The reaction mixture is brought to reflux and maintained for approximately 5 h.

The solvent is removed and the residue is taken up in 20 ml of CH_2Cl_2 and extracted with 20 ml of N/1 HCl. The acidic phase is basified while cold with a dilute sodium hydroxide solution to pH 12 and extracted with 3 times 20 ml of CH_2Cl_2. After washing, drying and removing the solvent, the residue is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 0.130 g of 3,4-dihydro-1'-(cyclopropylmethyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] is obtained. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.7.

The hydrochloride is prepared as described above. White powder, M.p. = 256°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.7.

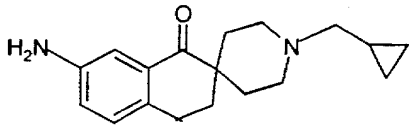
Analysis conforms to $C_{18}H_{23}ClN_2O_3$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.4 (m, 1H), 2-2.25 (m, 4H), 2.4-2.6 (m, 2H), 2.8-2.9 (m, 2H), 3.05-3.3 (m, 4H), 4.5-4.6 (m, 2H), 7.45 (d, 1H), 8.3 (d, 1H), 8.8 (s, 1H), 12.1 (1H))

IR: 2940, 2500, 2440, 1690, 1610, 1520, 1410, 1345, 1220, 1105, 960 cm^{-1}

EXAMPLE 14

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



60 mg (0.19 mmol) of 3,4-dihydro-1'-(methylcyclo-propyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine], obtained as described in Example 13, are dissolved in 1 ml of THF and then, with stirring, 0.21 g of tin chloride hydrate is introduced. The solution is brought to reflux for 1 h. The reaction liquors are charged to a saturated $NaHCO_3$ solution and extracted with 3 times CH_2Cl_2. The organic phase is washed and dried over Na_2SO_4. The solvent is evaporated and the residue obtained is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 29 mg of product are obtained.

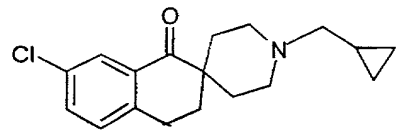
N.M.R.: $CDCl_3$ ^1H ((ppm): 0.1-0.2 (m, 2H), 0.4-0.55 (m, 2H), 0.85-1.0 (m, 1H), 1.6-1.7 (m, 2H), 1.9-2.1 (m, 4H), 2.3-2.4 (m, 2H), 2.5-2.75 (m, 4H), 2.8-2.9 (m, 2H), 3.6-3.8 (2H), 6.8 (d, 1H), 7.0 (d, 1H), 7.2 (s, 1H))

The hydrochloride is crystallized from ether. 26 mg of a yellow powder are obtained.

M.p. = 200°C, decomposition. TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.45.

EXAMPLE 15

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: Piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester.

60 g (0.381 mol) of ethyl isonipecotate and 400 ml of THF are placed in a three-necked flask which is protected from moisture and which is under an inert atmosphere, and 18.3 g (0.458 mol) of sodium hydroxide pellets are added. A solution of 100 g (0.458 mol) of di-*t*-butyl dicarbonate in 170 ml of THF is added over 1 h with stirring to the suspension. The temperature reaches 45°C. The reaction mixture is left stirring for 14 h at 20-25°C and is then poured onto 2 l of water and ice and extracted with 3 times 500 ml of ether. The organic phase is washed with 3 times 250 ml of a saturated NaCl solution, dried over Na_2SO_4 and concentrated. The residue is chromatographed by eluting with CH_2Cl_2 gradually

enriched with acetone and then distilled under a vacuum of 0.09 mm Hg and at a vapour temperature of 95-102°C. 82 g are obtained (Yd = 83.6%). TLC (95/5 CH_2Cl_2/acetone): Rf = 0.60.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.5-1.6 (m, 2H), 1.8-1.9 (m, 2H), 2.35-2.45 (m, 1H), 2.7-2.85 (m, 2H), 3.9-4.0 (m, 2H), 4.05-4.15 (q, 2H))

Stage 2: 4-(4-Chlorophenethyl)piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester

6.16 g (60.9 mmol) of diisopropylamine and 174 ml of THF, dried over molecular sieve, are introduced, by transfer under nitrogen, into a three-necked flask which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -10°C and 24.3 ml of 2.5N *n*-butyllithium in hexane (60.9 mmol) are run in. The mixture is stirred for 15 min at -10°C and cooled to -70°C, and a solution of 10.4 g (40.6 mmol) of the product from the preceding Stage 1 in 86 ml of THF is run in over approximately 20 min. The mixture is stirred for 10 min at -70°C and then 10.9 g (60.9 mmol) of HMPT are added. The mixture is kept stirring at -70°C for 1.5 h and a solution of 4-chlorophenethyl bromide (10.7 g, 48.7 mmol) in 86 ml of THF is run in over 20 min at -70°C. The mixture is stirred at 20-25°C for 14 h and then poured over 350 ml of water and extracted 3 times with ether. The organic phase is washed with an N/1 HCl solution and then with a saturated NaCl solution. After drying and concentrating, 17 g of an orange oil are obtained, which oil is chromatographed by eluting with CH_2Cl_2 gradually enriched with hexane, and then with acetone. 11.8 g are obtained (Yd = 80%). TLC (95/5 CH_2Cl_2/acetone): Rf = 0.70.

NMR: $CDCl_3$ ^1H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.0-2.1 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.9 (m, 2H), 3.7-3.9 (m, 2H), 4.05-4.15 (q, 2H), 6.9-7.0 (m, 2H), 7.1-7.2 (m, 2H))

Stage 3: Ethyl 4-(4-chlorophenethyl)piperidine-4-carboxylate

10.8 g of the product from the preceding Stage 2 and 50 ml of CH_2Cl_2 are introduced into a three-necked flask which is protected from moisture. The solution is stirred and 25 ml of trifluoroacetic acid are added at 20-25°C. The mixture is kept stirring for 30 min and then concentrated to dryness and the

residue is taken up in ether. The organic phase is washed with a 10% sodium hydroxide solution and then with a saturated NaCl solution. After drying and concentrating, 9 g of an oil are obtained, which oil crystallizes.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.45.

NMR: $CDCl_3$ ^1H ((ppm): 1.1-1.25 (t, 3H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.1-2.2 (m, 2H), 2.35-2.45 (m, 2H), 2.6-2.7 (m, 2H), 2.9-3.0 (m, 2H), 3.3 (1H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

Stage 4: Ethyl 1-(cyclopropylmethyl)-4-(4-chlorophenethyl)piperidine-4-carboxylate

3.4 g (11.5 mmol) of the product from the preceding Stage 3, 85 ml of THF, dried over molecular sieve, and then, with stirring, 14.9 ml of triethylamine and 2.4 ml (20.9 mmol) of 85% (bromomethyl)cyclopropane are successively introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. The mixture is brought to reflux for 14 h and then concentrated to dryness, and the residue is taken up in water and extracted twice with ether. The organic phase, washed with a saturated NaCl solution and dried, is concentrated. 3 g of crude product are obtained, which product is chromatographed (eluent: CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH). 2.6 g of oily product are obtained. Yd = 65%.

TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.50.

N.M.R.: $CDCl_3$ ^1H ((ppm): 0.0-0.1 (m, 2H), 0.35-0.45 (m, 2H), 0.7-0.8 (m, 1H), 1.1-1.2 (t, 3H), 1.4-1.5 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.1 (m, 2H), 2.1-2.2 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.85 (m, 2H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

Stage 5: 1-(Cyclopropylmethyl)-4-(4-chlorophenethyl)-piperidine-4-carboxylic acid

2.2 g (6.28 mmol) of the preceding ester and 6.6 ml of anhydrous dimethyl sulphoxide are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. A solution of potassium *t*-butoxide (4.4 g, 39 mmol) in 30 ml of dimethyl sulphoxide is added with stirring. The mixture is

left stirring for 2 h at 20-25°C. The reaction mixture is charged to 200 ml of water and then washed with ether. The aqueous phase is acidified to pH 5-7 with 10% HCl. The precipitate is filtered off and washed with water. The acid obtained is crystallized from a CH_2Cl_2/methanol mixture. M.p. = 250°C.

NMR: $CDCl_3$ ^1H ((ppm): 0.2-0.3 (m, 2H), 0.5-0.6 (m, 2H), 1.07-1.1 (m, 1H), 1.6-1.9 (m, 4H), 2.25-2.35 (m, 2H), 2.5-2.6 (m, 2H), 2.65-2.75 (m, 2H), 2.8-2.9 (m, 2H), 3.3-3.4 (m, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

IR: 3370, 1490, 1445, 1380, 1240, 1170, 1095, 965, 805 cm^{-1}.

Stage 6: 7-Chloro-3,4-dihydro-1'-(cyclopropylmethyl)-1-oxospiro[naphthalene-2(1*H*),4'-piperidine].

0.3 g (0.9 mmol) of the acid obtained previously and 6 ml of benzene are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. 0.24 g of PCl_5 and 6 ml of CH_2Cl_2 are added, followed by a further 0.24 g of PCl_5. The mixture is stirred for 2 h at 20-25°C. The mixture is cooled to 0°C, 0.44 ml of tin tetrachloride is introduced (copious precipitation), 12 ml of CH_2Cl_2 are added and the mixture is maintained at 0°C for 1 h and then at 20-25°C for 14 h. The solvents are removed and the residue is taken up in water. The aqueous phase is washed with ether and then basified to pH 12 with NaOH and extracted with ether. The organic phase is washed, dried and concentrated. The crude product is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 22 mg of product are obtained, which product is treated in solution in CH_2Cl_2 with 5N ethereal hydrochloric acid. After crystallization from ethyl acetate, the product is filtered off and dried at 50°C under vacuum.

White powder. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.55. M.p. = 263°C.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.3 (m, 1H), 2.0-2.15 (m, 4H), 2.4-2.55 (m, 2H), 2.8-2.9 (m, 2H), 2.95-3.05 (m, 2H), 3.1-3.3 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.3 (m, 1H), 7.4-7.5 (m, 1H), 7.9 (s, 1H), 12.2 (1H))

IR: 2930, 2440, 1720, 1490, 1230, 1185, 1095, 1025, 810 cm^{-1}.

EXAMPLES 16-34

Following the general procedures described above, the following additional compounds listed in table 1 were prepared.

Table 1

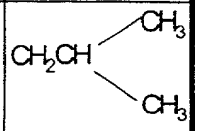
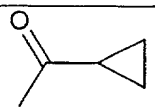
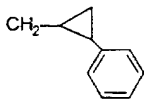
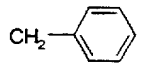
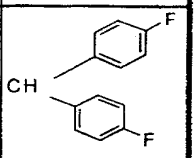
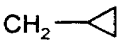
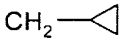
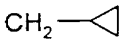
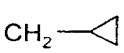
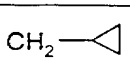
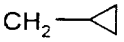
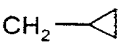
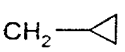
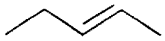
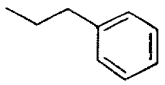
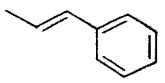
Example	R^1	R^2	R^3	R^4	A	R^5
16	=O		H	H	CH_2	CH_3
17	=O		H	H	CH_2	$CH_2CH=CH_2$
18	=O		H	H	CH_2	
19	=O		H	H	CH_2	
20	=O		H	H	CH_2	

Table 1 (cont.)

Example	R^1	R^2	R^3	R^4	A	R^5
21	=O		H	H	CH_2	
22	=O		H	H	CH_2	
23	H	OH	H	H	CH_2	

24	H	H	H	H	CH_2	
25	=O		H	H	Bond	
26	=O		H	H	CH_2CH_2	
27	=O		H	H		
28	=O		6-Cl	H	CH_2	
29	=O		6-F	H	CH_2	
30	=O		$6:OCH_3$	$7:OCH_3$	CH_2	
31	=O		H	H	CH_2	
32	=O		H	H	CH_2	
33	=O		H	H	CH_2	
34	=O		$6:OCH_3$	H	CH_2	

MP and NMR data for the compounds of examples 16 to 34 are provided below:

Example 16

MP = 240-243°C

R.M.N. $CDCl_3$ ^1H δ (ppm) Base:1,5-1,6 (m,2H); 1,95-2,05 (m,4H); 2,25 (s,3H); 2,3-2,4 (m,2H); 2,45-2,55 (m,2H); 2,9-2,95 (m,2H); 7,1-7,15 (m,1H); 7,2 - 7,25(m,1H); 7,35-7,4 (m,1H); 7,9-7.95 (m,1H)

Example 17

MP = 242-244°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl:2,05-2,15 (m,4H); 2,3-2,45 (m,2H); 3,0-3,1 (m,2H); 3,1-3,25 (m,2H); 3,35-3,5 (m,2H); 3,55-3,6 (m,2H); 5,4-5,55 (m,2H); 6,1 -6,25(m,1H); 7,2-7,35 (m,2H); 7,45-7.5 (m,1H); 7,9-7,95 (m,1H); 12,3-12,45 (m,1H)

Example 18

MP = 244-245°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,15 (d,6H); 2,0-2,1 (m,4H); 2,15-2,3 (m,1H); 2,55-2,65 (m,2H); 2,75-2,8 (m,2H); 2,95-3,0 (m,2H); 3,1-3,25 (m,2H); 3,35-3,45 (m,2H);7,2-7,35 (m,2H); 7,45-7.5 (m,1H); 7,9-7,95 (m,1H); 11,7-11,8 (m,1H)

Example 19

MP = 95-97°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 0,6-0,7 (m,2H); 0,8-0,95 (m,2H); 1,4-1,5 (m,2H); 1,6-1,7 (m,1H); 1,8-2,1 (m,4H); 2,9-3,5 (m,2H); 3,4-3,8 (m,4H); 7,1-7,3 (m,2H); 7,35-7.45 (m,1H); 7,9-8,0 (m,1H);

Example 20

MP = 220-221°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,05-1,3 (m,2H); 1,5-1,9 (m,1H); 2,0-2,2 (m,5H); 2,3-2,55 (m,2H); 2,9-3,4 (m,6H); 3,4-3,6 (m,2H); 7,0-7,6 (m,8H); 7,9-8,1 (m,1H); 12,2-12,4 (m,1H)

Example 21

MP = 261-262°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,0-2,1 (m,4H); 2,4-2,5 (m,2H); 2,95-3,05 (m,2H); 3,1-3,25 (m,2H); 3,3-3,4 (m,2H); 4,1-4,15 (m,2H); 7,2-7,35 (m,2H); 7,4-7,5 (m,4H); 7,65-7,7 (m,2H); 7,9-7,95 (m, 1H); 12,25-12,5 (m,1H)

Example 22

MP = > 250°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 1,4-1,55 (m,2H); 1,9-2,05(m,4H); 2,2-2,35 (m,2H); 2,4-2,55 (m,2H); 2,8-2,95 (m,2H); 4,2 (s,1H); 6,8-7,0 (m,4H); 7,15 (d,1H); 7,2-7,35 (m,5H); 7,4 (t,1H); 7,9 (d ,1H)

Example 23

MP = 91-93°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: -0,05-0,05 (m,2H); 0,35-0,45(m,2H); 0,7-0,85 (m,1H); 1,25-1,85 (m,7H); 2,2 (d,2H); 2,2-2,4 (m,2H); 2,5-2,6 (m,1H); 2,6-2,7 (m,3H); 4,2 (s,1H); 7,0- 7,3 (m ,4H)

Example 24

MP = 256-258°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 0,0-0,1 (m,2H); 0,4-0,5(m,2H); 0,75-0,85 (m,1H); 1,45-1,55 (m,4H); 1,6-1,65 (m,2H); 2,2 (d,2H); 2,35-2,6 (m,6H); 2,7-2,8 (m,2H); 6,9- 7,05 (m ,4H)

Example 25

MP= 241°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,0-0,15 (m,2H); 0,4-0,55 (m,2H); 0,75-0,9 (m,1H); 1,35 (d,2H); 1,9-2,15 (m,4H); 2,25 (d,2H); 2,9 (s,2H); 3,0 (d,2H); 7,25 (t,1H); 7,35 (d 1H); 7,5 (t,1H); 7,65 (d,1H); 12,1-12,2 (1H)

Example 26

MP = 242-243°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,7-0,8 (m,2H); 1,2-1,35 (m,1H); 1,85-2,0 (m,4H); 2,2-2,3 (m,2H); 2,3-2,4 (m,2H); 2,7-2,9 (m,6H); 3,4-3,5 (m,2H); 7,15-7,4 (m,4H);12,1-12,3 (1H)

Example 27

MP = 234°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 1,4(dd,3H); 1,85 (m,2H); 2,1 (m,3H); 2,3 (m,1H); 2,75 (m,2H); 2,9 (m, 2H) 3,25 (m,1H); 3,45-3,8 (m,3H); 7,3-7,45 (m,2H);7,6 (m,1H); 8,0 (dd,1H); 12,1 (1H)

Example 28

MP = > 250°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,1-2,2 (m,4H); 2,4-2,55 (m,2H); 2,9-2,95 (m,2H); 3,0-3,05 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 7,25-7,3 (m,2H);7,9,7,95 (m,1H); 12,2 (1H)

Example 29

MP = 227°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,0-2,2 (m,4H); 2,4-2,6 (m,2H); 2,85-2,95 (m,2H); 3,0-3,1 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 6,9-7,0 (m,1H); 7,0-7,1 (m,1H); 7,95-8,05 (m,1H); 12,1 (1H)

Example 30

MP = 229°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 2,15 (m,4H); 2,45 (td,2H); 2,9 (m,2H); 2,95 (m, 2H); 3,3 (m,2H); 3,55 (m,2H); 4,85 (s,3H); 4,95 (s,3H); 6,65 (s,1H); 7,45 (s,1H); 12,05 (1H)

Example 31

M P = 189-192°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,2-0,3 (m,1H); 0,6-0,7 (m,1H); 0,7-0,8 (m,1H); 0,8-0,9 (m,1H); 1,1-1,2 (m,1H); 1,55 (d,3H); 1,6-1,7 (m,1H); 2,1-2,2 (m,4H); 2,5-2,7 (m,2H); 3,0-3,1 (m,2H); 3,3-3,6 (m,4H); 7,2-7,25 (m,1H); 7,3-7,35 (m,1H); 7,45-7,5 (m1H); 8,0-8,05 (m,1H); 11,85 (1H)

Example 32

M P = > 235°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,7 (d,3H); 2,1-2,2 (m,4H); 2,4-2,5 (m,2H); 2,6-2,7 (m,2H); 2,9-3,1 (m,4H); 3,2-3,3 (m,2H); 3,4-3,5 (m,2H); 5,3-5,4 (m,1H);5,6-5,7 (m,1H); 7,2-7,3 (m,1H); 7,3-7,35 (m,1H); 7,5-7,6 (m1H); 7,95-8,0 (m,1H); 12,2 (1H)

Example 33

M P = 209°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,1 (m,4H); 2,25 (m,2H); 2,45 (m,2H); 2,7 (m,2H); 2,9 (m, 2H); 3,0 (m,2H); 3,15 (m,2H); 3,4 (m,2H); 7,1-7,35 (m,7H); 7,5 (m,1H); 7,95 (m,1H); 11,95 (1H)

Example 34

M P = 228°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,0-2,2 (m,4H); 2,4 (td,2H); 3,0 (m,2H); 3,3 (qd, 2H); 3,45 (m,2H); 3,75 (t,2H); 3,85 (s,3H); 6,55 (qt,1H); 6,7 (m,2H); 6,85 (dd,1H); 7,35 (m,3H); 7,45 (d,2H); 7,95 (d,1H); 11,95 (1H).

EXAMPLES 35-69

Following procedures known in the art, some of the tetralones described above were alkylated to yield the following additional compounds listed in table 2.

Table 2

Ex.	R^1-R^2	R_3	R_4	R_5	A	Rf
35	=O	5:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.7
36	=O	5:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.5
37	=O	5:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.8
38	=O	5:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.7
39	=O	5:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.7

40	=O	5:OCH_3	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.55
41	=O	5:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.90
42	=O	6:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.4
43	=O	6:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.3
44	=O	6:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.55
45	=O	6:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.5
46	=O	6:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.5
47	=O	6:OCH_3	**H**	CH_2-CH_2-CH_2-C_6H_6	CH_2	**0.4**
48	=O	6:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.7
49	=O	7:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.5
50	=O	7:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.2
51	=O	7:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.4
52	=O	7:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.4
53	=O	7:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.4
54	=O	7:OCH_3	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.3
55	=O	7:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.65

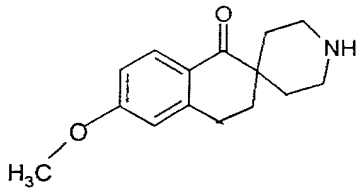
Table 2 (cont.)

Ex.	**R^1-R^2**	**R_3**	**R_4**	**R_5**	**A**	**Rf**
56	=O	H	H	$(CH_2)_2$-c-C_3H_5	$CHCH_3$	0.4
57	=O	H	H	CH_2-c-C_4H_7	$CHCH_3$	0.2
58	=O	H	H	CH_2-c-C_6H_{11}	$CHCH_3$	0.5
59	=O	H	H	CH_2-CH=CH-C_6H_6	$CHCH_3$	0.45
60	=O	H	H	CH_2-CH_2-C_6H_6	$CHCH_3$	0.5
61	=O	H	H	CH_2-CH_2-CH_2-C_6H_6	$CHCH_3$	0.4
62	=O	H	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	$CHCH_3$	0.7
63	=O	6:Cl	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.5

64	=O	6:Cl	H	CH_2-c-C_4H_7	CH_2	0.3
65	=O	6:Cl	H	CH_2-c-C_6H_{11}	CH_2	0.65
66	=O	6:Cl	H	CH_2-CH=CH-C_6H_6	CH_2	0.55
67	=O	6:Cl	H	CH_2-CH_2-C_6H_6	CH_2	0.65
68	=O	6:Cl	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.5
69	=O	6:Cl	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.85

EXAMPLE 70

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The synthesis is similar to the one described in example 1 except in stage 3 wherein 6-methoxytetralone is used instead of 1-tetralone.

N.M.R.: $CDCl_3$ ^1H ((ppm) Base: 1.9-2.3 (m, 6H); 2.9-3.1 (m, 2H); 3.3-3.6 (m, 4H); 3.85 (s, 3H); 6.65 (s, 1H); 6.8-6.9 (m, 1H); 7.9-8.0 (dd, 1H); 9.5 (bs, 2H)).

M.P. = 236-237°C, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.25.

IR: 2724, 1657, 1595, 1446, 1258, 1223, 1086, 978, 906, 839 cm^{-1}

As noted above, the invention compounds of Formula I are useful for treating chronic pain and other CNS disorders such as seizures, e.g. epilepsy. The compounds have been evaluated in standard assays to measure their ability to block isolated mammalian Na neuronal channels, as well as their ability to antagonize prostaglandin E_2 (PGE_2) production. Both assays are routinely utilized to indicate clinical utility of compounds for treating chronic pain and other CNS disorders (see Tonelian *et al.*, Anesthesiology, **24**: 949-951, 1991).

EXAMPLE 71

Sodium channel [^{3}H] batrachotoxin (BTX) binding assay

Cerebral cortices from male Sprague-Dawley rats were homogenized in a glass-Teflon homogenizer in 10 volumes of ice-cold 0.32 M sucrose, 5 mM K_2HPO_4 (pH 7.4 at 4°C). The homogenate was centrifuged at 1000 g. for 10 min, the pellet was resuspended in the same volume of sucrose and recentrifuged. The pellet was discarded and the two supernatants resulting from these two centrifugations were pooled and centrifuged at 20000 g. for 10 min. The resulting pellet was resuspended in a Na-free assay buffer containing 50 mM HEPES, 5.4 mM KCl, 0.8 mM $MgSO_4$, 5.5 mM glucose and 130 mM choline chloride (pH 7.4 at 25°C). Binding assay were initiated by the addition of 150-200 µg synaptosomal protein to an assay buffer containing 25 µg scorpion venom (Leirus quinquestriatus), 0.1% BSA and 10 nM [^{3}H] batrachotoxin (40 Ci/mmol, NEN) in the presence or absence of different concentrations of unabelled drugs (250 µl final volume). Non-specific binding was determined in the presence of 0.3 mM veratridine. Reactions were incubated for 90 min at 25°C and bound ligand was separated from free by vacuum filtration through Whatman GF/B filters; the filters were washed with 2x5 ml buffer (5 mM HEPES, 1.8 mM $CaCl_2$, 0.8 mM $MgSO_4$, 130 mM choline chloride, 0.01% BSA ; pH 7.4 at 25°C) and bound ligand was estimated by liquid scintillation spectrometry.

EXAMPLE 72

$^{22}Na^+$ influx into SK-N-SH neuroblastoma cells

Characterization of Na^+ channels activity is performed using human SK-N-SH cells in 96-well culture plates. The effect of tested compounds on Na^+ influx through the Na^+ channels is evaluated under stimulation by veratridine.

SK-N-SH cells are preincubated for 15 min at 37°C in the presence of test compounds in a 25 mM hepes/Tris pH 7.5 buffer containing 5.4 mM KCl, 0.8 mM $MgSO_4$, 1.8 mM $CaCl_2$, 5mM glucose, 0.1% BSA, 140 mM choline chloride.

The influx of Na^+ is induced by the incubation for 10 min at 37°C of SK-N-SH cells in the presence of test compound and veratridine in the incubation buffer supplemented with 1 µM ouabaine, 10 mM NaCl, 130 mM choline chloride and $^{22}Na^+$ (Jacques, Y, Fosset, M. and Lazdunski, M., (1978), Molecular properties of the action potential Na+ ionophore in neuroblastoma cells. J. Biol. Chem., 253, 7383-7392).

Following this $^{22}Na^+$ uptake, cells are washed with 0.1 mM $MgCl_2$. The radioactivity is then measured with a microplate reader (Topcount, Packard) after the addition of a scintillation liquid (Microscint 40, Packard).

The reference compound is tetrodotoxin tested at 7 concentrations ranging from 10^{-10}M to 10^{-7} M in order to determine an IC_{50} value.

EXAMPLE 73

Analgesic activity on chronic hyperalgesia induced by PGE_2 in rats

The test consists in determining the analgesic effect of the test compound in rats by the Randall and Selitto test, in which chronic hyperalgesia has been triggered by intraplantar injection of PGE_2 over 4 days into a leg, according to a protocol adapted from Nakamura-Craig *et al* (Pain, **63**: 33-37, 1995).

The study is carried out on batches of 120-140 g Sprague-Dawley rats to which 100 ng of PGE_2 is administered in a volume of 100 µl by the intraplantar route, for 4 consecutive days twice a day; this causes chronic hyperalgesia in the leg from the 5th day, for at least one week. On the day of the test, in the morning, the threshold of reaction to pain is checked by the Randall and Selitto test, and animals whose threshold is ψ100 arbitrarily defined units are selected. In the afternoon, the measurement is repeated after prior administration by the s.c. route of a solution of the test compound; this administration is carried out 30 min before measuring the pain threshold. For each batch, the analgesic activity (%) is

calculated from the means of the thresholds measured before and after treatment, as compared with that of the control animals, who received only the vehicle.

The following Table 3 lists the Na channel binding and the analgesic activities of representative compounds of the invention when measured in the foregoing assays.

Table 3: Pharmacological activities

Compound of Example No	[^{3}H] BTX assay: Na^+ channel binding Ki (nM)	^{22}Na influx IC50 (µM)	PGE_2 assay: Analgesic activity at 10 mg/kg S.C. (%)
2	876	10.7	49
6	1435	3.4	67
7	366	0.94	57
8	397	0.97	47
10	3890	30	100
33	291	1.2	81
36	475	3.4	51
42	ND	4.3	46
43	ND	6	39
47	ND	0.6	66
49	2183	7.6	38
70	ND	ND	46

The foregoing biological data establish that the compounds of Formula I are particularly useful for treating CNS disorders in mammals, especially neuropathic pain, trigeminal neuralgia, diabetic neuropathy, sciatic neuropathy and seizures. The compounds are particularly well suited to the treatment of diabetic neuropathy, which is the most common complication accompanying diabetes mellitus. The compounds also are useful for prophylaxis and treatment of migraine.

The invention compounds can be administered to humans who are in need of treatment for a chronic pain condition or seizure disorder by both the oral and parenteral routes, for instance as tablets or capsules, or as subcutaneous or intravenous injections. The compounds will be administered in an amount which is effective to control and treat the seizure disorder or relieve the neuropathic pain sensation. Such effective amounts will generally be from about 0.1 to about 2000 mg/kg of mammalian body weight. Commonly prescribed doses will be from about 5 mg/kg to about 500 mg/kg. Such dosage amounts can be administered to adult humans from 1 to 4 times a day for the relief of neuropathic pain and seizure disorders. The precise dose to be employed will depend upon the specific compound of Formula I utilized, the particular condition of the subject being treated, and generally will be dictated by the attending physician or other medical practitioner.

The compounds can be formulated by normal methods for convenient oral or parenteral dosing. Typical oral forms are tablets, capsules, troches, elixirs, syrups, suspensions, and controlled sustained release forms, for example through osmotic pumps. The compounds can likewise be formulated for administration intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. The compounds are formulated by using conventional diluents, excipients, carriers and binders routinely used in the phamaceutical art. For example, the compounds can be admixed with carriers, diluents and excipients such as starch, cellulose, PVP, methylcellulose, sugar, wax, talc, and with stabilizers and binders such as Mg stearate, MgO, $CaCO_3$, methyl-*p*-hydroxybenzoate (methylparaben), and *n*-propyl-*p*-hydrobenzoate (propylparaben).

The following additional examples illustrate typical pharmaceutical formulations which are provided by this invention.

EXAMPLE 74

Tablet Preparation

Compound of Example 10	25.0 mg
Microcrystalline cellulose	50.0 mg
Modified food corn starch	50.0 mg
Magnesium stearate	1.0 mg

The above ingredients are blended to uniformity and compressed into a tablet. Such tablets are administered at the rate of 1 to 4 times a day to a human suffering from chronic pain.

EXAMPLE 75

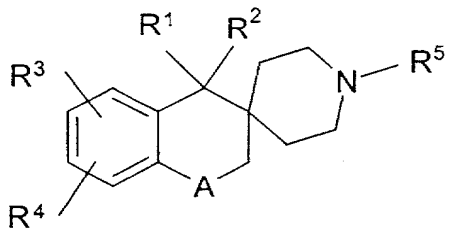
Intravenous Preparation

Compound of example 2	400 mg
Acetate buffer	20 ml
dil aqueous HCl or NaOH	to pH6.5
Sterile isotonic saline	qs 1000 ml

The invention compound is dissolved in the acetate buffer and the pH is adjusted to 6.5. Isotonic saline is added to a volume of 1000 ml. The solution is filled into a sterile flexible plastic container equipped with a drip tube. The solution is administered IV to a patient suffering from diabetic neuropathy.

What is claimed is :

1. A tricyclic compound of Formula I:



(I)

wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen or hydroxy; or

R^1 and R^2 together are oxygen ;

A is a bond, CH_2, CH CH_3, CH_2 CH_2 or $C(CH_3)_2$;

R^3 and R^4 are the same or different and are hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, trifluoromethyl, NO_2, COR^6, $COOR^6$ or NR^6R^7, wherein R^6 and R^7 are the same or different and are hydrogen, C_1-C_6 alkyl or benzyl ;

R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, (O=C)-C_{1-6} alkyl, (O=C)- C_{2-6} alkenyl, (O=C)-C_{3-6} cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl, and a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein R^5 is C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

3. A compound according to Claim 1 or 2, wherein R^3 is hydrogen, halogen or C_{1-4} alkoxy.

4. A compound according to any one of Claims 1 to 3, wherein R^1 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl, optionally substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl, and R^2 is hydrogen.

5. A compound according to any one of Claims 1 to 4, wherein R^4 is hydrogen.

6. A compound selected from the group consisting of:
3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;

3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

7. A compound selected from the group consisting of:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

8. A compound selected from the group consisting of :

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

9. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 8 admixed with a pharmaceutically acceptable carrier, diluent, or carrier therefor.

10. A method for treating a mammal suffering from pain and in need of treatment comprising administering an effective amount of a compound of any one of Claims 1 to 8.

11. A method according to Claim 10 wherein the pain is neuropathic pain.

12. A method according to Claim 10 wherein the pain is diabetic neuropathy.

13. A method for treating a mammal suffering from a seizure disorder comprising administering an effective amount of a compound of any one of Claims 1 to 8.

POWER OF ATTORINEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number)*

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I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/137,868	**07 June 1999**
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

PCT/EP00/05783	**07 June 2000**	**Pending**
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Express Mail No. EF378134286US

Docket No.
5808-01-SD

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TRICYCLIC ANALGESICS

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ As United States Application No. _____ or PCT International Application Number _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐